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LETTER TO THE EDITOR

Hippocampal Theta Frequency and Novelty

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To the Editor:

Various studies indicate that the hippocampus plays an essential role in novelty detection. In particular, contextual/spatial changes are detected by the hippocampus, presumably by comparing incoming information with stored information (e.g., Knight, 1996). However, the exact nature and processes underlying hippocampal novelty detection remain elusive. One important mechanism that may underlie hippocampal novelty detection is hippocampal theta activity. In a recent paper, Jeewajee et al. (2008) proposed a link between the hippocampal theta and the detection of novel contexts. Four food-deprived rats were equipped with hippocampal electrodes and exposed to familiar and novel environments in which they were searching for food. The authors found that the peak hippocampal theta frequency dropped (by about 0.6 Hz) when the rats were tested in a novel environment. They argued that the change in theta frequency may function as a novelty signal because hippocampal theta frequency is the same in the whole hippocampus (Buzsaki, 2002) and suggested that this reduction in the theta frequency would have implications for memory encoding. The authors speculate that novelty leads to an altered weighing between a high-frequency locomotion-related theta and a low-frequency theta dependent on acetylcholine release. Although the study of Jeewajee et al. (2008) provides novel insights into the mechanisms underlying hippocampal novelty detection, some points suggest that it may be too early to accept their conclusions at face value.

The first point is related with the design of study, in which food-deprived rats were used. During the recording sessions, rats were foraging grains of sweetened rice which were thrown in the box every 30 s. Several studies have indicated that food consumption and reinforcement increase hippocampal acetylcholine (ACh) levels (Ghiani et al., 1998; Iso et al., 1999). Since specific assumptions were made with respect to hippocampal ACh levels and novelty-induced increase in ACh and an increase in cholinergic input to the hippocampus affects hippocampal theta activity (Givens and Olton, 1995; Podol'skii et al., 2001), the results of this experiment may have been distorted by the foraging. Therefore, it would have been more appropriate to expose nondeprived subjects to familiar and novel environments. This may be a more proper setting to detect changes in theta in relation to novelty per se.

Secondly, the authors found the effects of novelty on peak theta frequency, but not on theta power. This is at odds with previous findings in the literature. Jeewajee et al. relate their findings of novelty-induced theta peak frequency reductions to a study of Givens and Olton (1995). In this study, carbachol injections into the medial septum, which increases hippocampal ACh levels, did not affect the theta peak. Only in combination with scopolamine (given intraperitoneal), the peak theta frequency was reduced by carbachol injections. Two other studies of this group (Givens and Olton, 1994; Markowska et al., 1995) also examined the effects of intraseptal injection of cholinergic drugs. These studies indicate that scopolamine (i.e., lower hippocampal ACh) reduces theta power and increases peak frequency. Further, the muscarinic agonist oxotremorine reduced peak frequency and increased theta power. In all these studies, decreases and increases in theta power were very robust, while effects on peak frequency were smaller and less consistent. The decrease in peak frequency found by Jeewajee et al. is thus in line with previous data, but their lack of effects of novelty on theta power is puzzling. Indeed, we recently conducted a study in which rats were exposed to novel and familiar environments. We found that theta power was affected by novelty rather than theta frequency (see Fig. 1).

The third point of caution relates to the analysis of theta frequency. Jeewajee et al. showed changes in theta frequency as accurate as 0.2 Hz. Frequency resolution, the accuracy of different frequency steps that can be analyzed, depends on the length of a measurement and the sample rate; the longer and higher, respectively, the better will be the resolution. In the study of Jeewajee et al., the sample rate that was used to record the EEG was 250 Hz. With these settings, epochs of 5 s are needed to obtain a frequency resolution at a 0.2 Hz level. Unfortunately, the authors did not provide any specific information on how long animals usually spent running at speeds over 5 cm/s and their restriction for the acceptance of an epoch into

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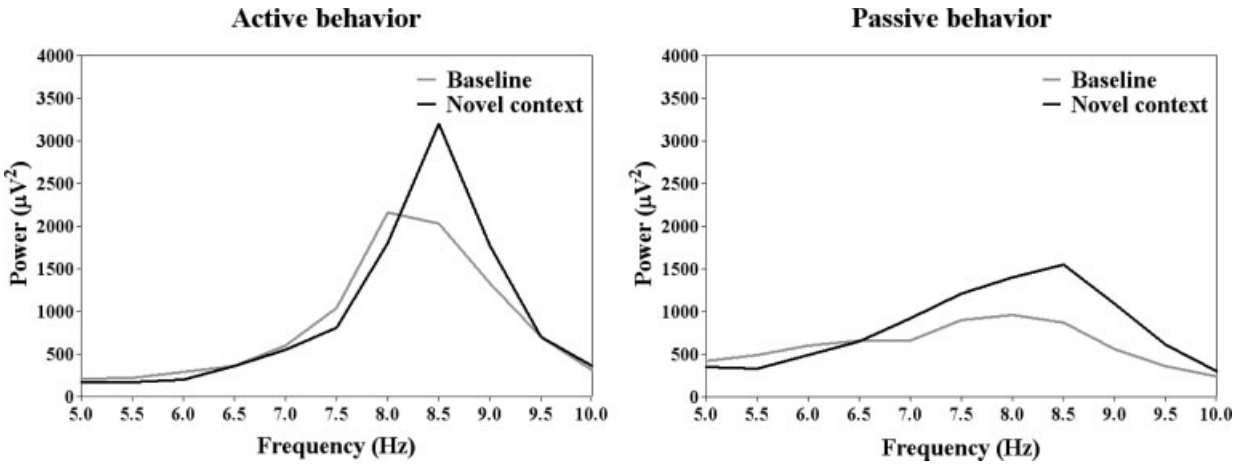

FIGURE 1. Theta power during active (rearing and running) and passive (sitting quietly) behavior in the rat. In this study, animals (n = 10; equipped with bipolar electrodes; see Sambeth et al., 2007) were first placed in a familiar environment for 3 min, followed by placement in a novel environment 1 h later. Epochs of 1,300 ms were sampled at 1,024 Hz with a band-pass filter of 1–100 Hz, ensuring a frequency resolution of 0.5 Hz. A Fast Fourier Transform was performed to calculate the power spectra. Theta activity was measured between 5 and 10 Hz from the dorsal hippocampus. Theta power was significantly larger in the novel than in the familiar environment, irrespective of the type of physical activity ($F_{1,9}$ = 6.81, P < 0.028 for active and $F_{1,9}$ = 6.64, P < 0.03 for passive behavior). Theta frequency was not significantly changed (Fs < 3.9).

the analysis (only epochs >500 ms). It is therefore not clear whether the resolution they present is feasible.

The fourth point relates to the proposed mechanism. Jeejawee et al. proposed that theta frequency is determined by a location-induced oscillation at 8–9 Hz, and a cholinergically mediated oscillation at 6–7 Hz. Novelty would result in increased cholinergic release in the hippocampus, and thus bias the theta rhythm toward the lower frequency associated with acetylcholine. However, if these two rhythms would coexist, one would not observe one peak in the power spectrum that shifts with novelty, but two peaks that would have different size in different conditions. Moreover, in our experiment, we did not find an increase in peak theta frequency when animals were in locomotion relative to when they were passive (see Fig. 1). Instead, it was again theta power that differentiated active from passive behavior, with novelty increasing power at both levels of activity.

Taken together, these comments suggest caution in concluding that a lower theta peak frequency reflects novelty detection. Previous data and data from our pilot study hint toward a novelty-induced increase in hippocampal theta power. Moreover, a model in which hippocampal theta results from two oscillations does not seem to produce the data pattern found by the authors. Nevertheless, both their and our findings suggest that theta oscillations are affected by novelty, and we agree with the authors that this probably has consequences for our understanding of hippocampal learning. Since both ACh release and theta oscillations are affected by a range of factors, testing animals in more settings may be needed to elucidate the nature of novelty effects on hippocampal theta oscillations.

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